(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 526 658 A1**

(12) **EUROPEAN PATENT APPLICATION published in accordance with Art. 158(3) EPC**

(21) Application number: **92905305.6**

(22) Date of filing: **24.02.92**

(86) International application number: **PCT/JP92/00189**

(87) International publication number: **WO 92/14719 (03.09.92 92/23)**

(51) Int. Cl.[5]: **C07D 277/34**, C07D 417/12, A61K 31/425, A61K 31/44

(30) Priority: **25.02.91 JP 53275/91**
21.02.92 JP 72496/92

(43) Date of publication of application: **10.02.93 Bulletin 93/06**

(84) Designated Contracting States: **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

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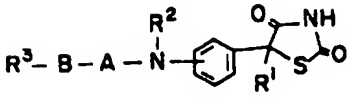
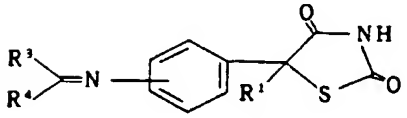
(54) **THIAZOLIDINE-2,4-DIONE DERIVATIVE, SALT THEREOF, AND PRODUCTION OF THE SAME.**

(57) A novel thiazolidine-2,4-dione derivative with hypoglycemic and aldose reductase inhibitory activities, represented by the general formula (1) or (2), a salt thereof, a process for producing the same, and a medicine containing the same, wherein R^1 and R^2 may be the same or different from each other and each represents hydrogen or lower alkyl; R^3 represents phenyl naphthyl, benzoyl, 5- or 6- membered heterocycle or a benzene-containing condensed ring thereof, all of which may have at least one substituent; A represents carbonyl, sulfonyl or a free bond; and B represents lower alkylene, lower alkenylene or a free bond, in formula (2) R^4 represents hydrogen or lower alkyl, and R^1 and R^3 are as defined above.

EP 0 526 658 A1



(I)



(2)

Technical field

The present invention relates to novel thiazolidine-2,4-dione derivatives prossesing blood sugar-lowering action and aldose reductase-inhibitory action, their salts, their preparation processes and a drug containing them.

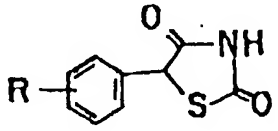
Background techniques

As therapeutic agents for diabetes, various biguanide type and sulfonylurea type compounds have been used so far. However, the biguanide type compounds cause the lactic acid acidosis and the sulfonylurea type compounds cause serious hypoglycemia posing a problem on their adverse effect, thus the advent of therapeutic agent for diabetes without such defect is desired.

On the other hand, it has been made clear that the aldose reductase takes part in the crisis of diabetic complication (J.H. Kinoshita et al, J. Am. Med. Assoc. 246, 257 (1981)). Thus inhibition of the aldose reductase may bring prevention and therapy of diseases occurring as diabetic complications.

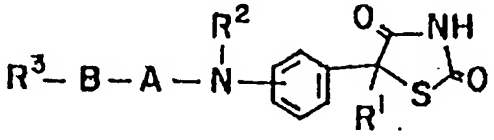
Compounds possessing blood sugar-lowering action and compounds possessing inhibitory action of aldose reductase have been extensively searched each separately.

For example, as the aldose reductase-inhibitory agents, particular thiazolidine-2,4-dione derivatives are already publicly known (Japanese Unexamined Patent Publication No. Sho 57-28073, Chem. Pharm. Bull. 30(10), 3601, (1982)). Namely, it is publicly known that 5-phenylthiazolidine-2,4-dione derivatives represented by a general formula



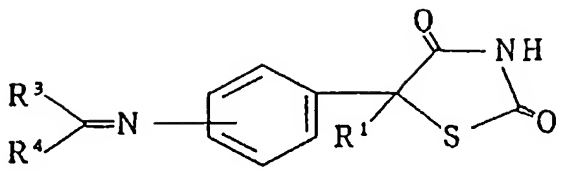
[wherein R denotes a hydrogen atom, lower alkyl group, hydroxyl group, alkoxy group, nitro group, amino group, lower acylamino group, halogen or trifluoromethyl group], have aldose reductase-inhibitory action.

However, thiazolidine-2,4-dione derivatives of the present invention represented by a general formula (1)



(I)

[wherein R^1 and R^2 each independently represent hydrogen atoms or lower alkyl groups, R^3 denotes a phenyl group, naphthyl group, benzoyl group or 5-membered or 6-membered heteroring and its benzene-condensed ring, which may have one or more substituents, A denotes a carbonyl group, sulfonyl group or bonding hand, and B denotes a lower alkylene, lower alkenylene or bonding hand], or their salts and thiazolidine-2,4-dione derivatives of the present invention represented by a general formula (2)



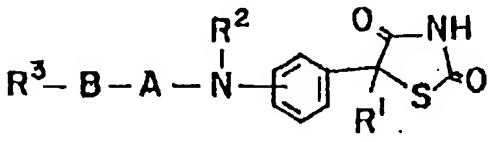
(2)

[wherein R^4 denotes a hydrogen atom or lower alkyl group, and R^1 and R^3 are same as above], were not known at all, and also it could not be anticipated that thiazolidine-2,4-dione derivatives of the present invention had superior blood sugar-lowering action together with strong aldose reductase-inhibitory action.

The purpose of the present invention is to provide compounds having superior blood sugar-lowering action and simultaneously strong aldose reductase-inhibitory action and being useful as effective and highly-safe drugs capable of preventing and treating diabetes and complication thereof.

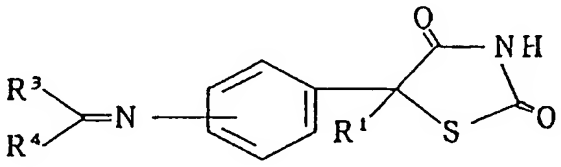
Disclosure of the invention

As a result of diligent studies for solving such problems, the inventors have found that thiazolidine-2,4-dione derivatives represented by the general formula (1)



(1)

[wherein R^1 and R^2 each independently represent hydrogen atoms or lower alkyl groups, R^3 denotes a phenyl group, naphthyl group, benzoyl group or 5-membered or 6-membered heteroring and its benzene-condensed ring, which may have one or more substituents, A denotes a carbonyl group, sulfonyl group or bonding hand, and B denotes a lower alkylene, lower alkenylene or bonding hand], or their salts and thiazolidine-2,4-dione derivatives represented by the general formula (2)



(2)

[wherein R^4 denotes a hydrogen atom or lower alkyl group, and R^1 and R^3 are same as above], or their salts have superior blood sugar-lowering action together with aldose reductase-inhibitory action, leading to the completion of the present invention.

For the "lower alkyl" shown in the present invention, straight chain or branched ones with carbon atoms of 1 to 6 such as methyl, ethyl, n-propyl and i-propyl are exemplified.

For the "substituent" in "phenyl group, naphthyl group, benzoyl group or 5-membered or 6-membered heteroring and its benzene-condensed ring, which may have one or more substituents", hydrogen atom,

halogen, lower alkyl group, hydroxyl group, lower alkoxy group, nitro group, amino group (said amino group may be substituted with lower alkyl group, lower alkanoyl group or benzoyl group), phenyl group(this phenyl group may be substituted with halogen, lower alkyl group or lower alkoxy group), lower alkanoyloxy group, carboxyl group, methylenedioxy group, sulfamoyl group (this sulfamoyl group may be substituted with lower alkyl group), trifluoromethyl group, or the like can be mentioned. For "halogen", fluorine, chlorine, bromine and iodine are exemplified.

For "lower alkoxy", straight chain or branched ones with carbon atoms of 1 to 6 such as methoxy, ethoxy, n-propoxy and i-propoxy are exemplified. For "lower alkanoyl", ones with carbon atoms of 1 to 4 such as acetyl and propionyl are exemplified. For "lower alkanoyloxy", ones with carbon atoms of 1 to 4 such as acetyloxy and propionyloxy are exempified.

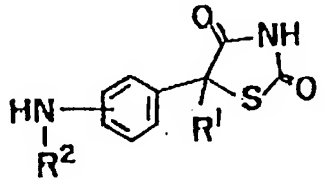
The "5-membered or 6-membered heteroring and its benzene-condensed ring" mean saturated or unsaturated monocyclic or polycyclic heterocyclic groups capable of containing one or more nitrogen, oxygen and sulfur atoms and, piperidyl, piperazinyl, furyl, thienyl, imidazolyl, thiazolyl, pyridyl, benzofuryl, benzothienyl, indolyl, quinazolyl, etc. can be exepmlified.

"Lower alkylene" means ones with carbon atoms of 1 to 6 and methylene, ethylene, trimethylene, etc. are exemplified. "Lower alkenylene" applied similarly to "lower alkylene" but has carbon atoms of 2 to 6 and unsaturated bond(s).

The "eliminating group" is halogen, lower alkoxy or hydroxy and preferable one is halogen. "Their salts" mean salts admissible as drugs and, for example, salts with cations such as sodium and potassium or with inorganic acids (hydrochloric acid, sulfuric acid, etc.) or organic acids (p-toluenesulfonic acid etc.) can be included.

The compounds of the present invention can be prepared through processes shown below.

(A) Compounds represented by the general formula (1) can be obtained by reacting compounds represented by a general formula (3)



(3)

[wherein R^1 and R^2 are same as above],
with compounds represented by a general formula (4)

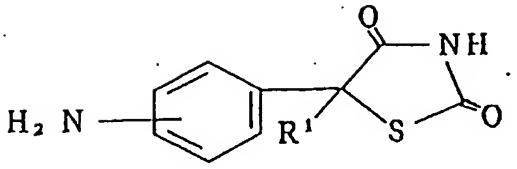
R^3 - B - A - Z (4)

[wherein R^3, A, Z and B are same as above],
in the presence of suitable base or condensing agent.

This reaction can be conducted beneficially in a solvent such as dioxane, dimethylformamide or ethyl acetate in the presence of alkali metal hydride such as sodium hydride, for example, alkali metal hydroxide such as sodium hydroxide, for example, alkali metal carbonate such as potassium carbonate, for example, or organic base such as pyridine or triethylamine, for example, as a base.

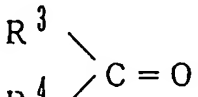
For the condensing agents, for example, dicyclohexylcarbodiimide, diethylphosphoryl cyanide, etc. are exemplified. The reaction temperature is within a range from 0 to 120 °C and the reaction completes for 1 to 5 hours.

(B) Compounds represented by the general formula (2) can be obtained by condensing compounds represented by a general formula (3a)



(3a)

[wherein R^1 is same as above],
or their salts with compounds represented by a general formula (5)



(5)

[wherein R^3 and R^4 are same as above].

This reaction can be conducted in a solvent inert to reaction such as ethanol, toluene or xylene, for example, in the presence of, for example, p-toluenesulfonic acid or the like as a catalyst or in the absence of catalyst. The reaction is conducted within a range from room temperature to boiling point of solvent and the reaction completes for 1 to 5 hours.

(C) Among compounds represented by the general formula (1), such compounds that R^2 is hydrogen atom, A is bonding hand and B is lower alkylene can also be obtained by reducing compounds represented by the general formula (2).

This reaction can be conducted in a solvent inert to reaction such as methanol, ethanol, ether or tetrahydrofuran, for example in the presence of, for example, sodium borohydride, lithium aluminum hydride or the like as a reducing agent. The reaction is conducted within a range from 0 °C to boiling point of solvent and the reaction completes for 1 to 5 hours.

The compounds obtainable through said processes can be isolated and purified by publicly known separation and purification means, for example, solvent extraction, recrystallization, chromatography, etc.

If pharmaceutically admissible salts of compounds represented by the general formula (1) or general formula (2) are further needed, they can be obtained by reacting with cation-copossessing bases such as sodium hydroxide and potassium hydroxide, for example, inorganic acids such as hydrochloric acid and sulfuric acid, for example, and organic acids such as fumaric acid and oxalic acid, for example.

Moreover, because the inventive compounds represented by the general formula (1) and general formula (2) have one or more asymmetric carbon atoms, these exist optical isomers, but the invention also includes those optical isomers and racemic modifications.

Embodiment to put the invention into practice

The preparative examples and examples of the inventive compounds will be described to illustrate the invention in more detail.

Example 1

5-(4-Benzoylaminophenyl)thiazolidine-2,4-dione

Into 20 ml of dioxane were dissolved 0.5 g of 5-(4-aminophenyl)thiazolidine-2,4-dione, and, after added 0.34 g of benzoyl chloride and further added dropwise 0.24 g of triethylamine, the mixture was refluxed for 1 hour. After cooling by standing, the reaction mixture was poured into 150 ml of ice water and the crystals deposited were collected by filtration, washed with water and dried. These were recrystallized from

chloroform to obtain 0.70 g of title compound.
m.p. 240.0 - 245.0 °C

Elemental analysis (%) As $C_{16}H_{12}N_2O_3S$			
Calculated	C 61.53	H 3.87	N 8.97
Observed	C 61.65	H 3.88	N 8.75

Example 2

5-(4-Piperonyloylaminophenyl)thiazolidine-2,4-dione

Into 20 ml of dimethylformamide were dissolved 1.00 g of 5-(4-aminophenyl)thiazolidine-2,4-dione and 0.80 g of piperonylic acid, and, after added 1.12 g of diethylphosphoryl cyanide and then 0.50 g of triethylamine at 0 °C, the mixture was stirred for 1 hour as it was. Thereafter, the reaction mixture was brought to room temperature and stirred for 2 hours. Then, it was poured into 200 ml of water and, after made acidic with hydrochloric acid, the crystals deposited were collected by filtration. These were recrystallized from ethanol to obtain 1.05 g of title compound.
m.p. 275.0 - 277.0 °C

Elemental analysis (%) As $C_{17}H_{12}N_2O_5S$			
Calculated	C 57.30	H 3.39	N 7.86
Observed	C 57.39	H 3.28	N 7.81

Example 3

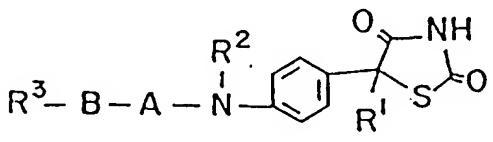
5-(4-(p-Toluenesulfonylamino)phenyl)thiazolidine-2,4-dione

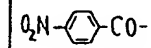
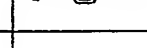
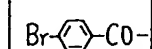
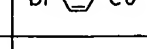
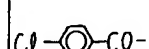
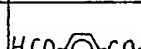
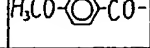
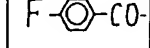
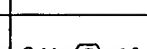
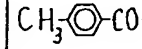
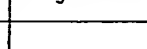
Into 10 ml of pyridine were dissolved 0.50 g of 5-(4-amino-phenyl)thiazolidine-2,4-dione, and after added 0.46 g of p-toluenesulfonyl chloride, the mixture was stirred for 1 hour at room temperature. After the completion of reaciton, the reaction mixture was poured into ice water, which was extracted with ethyl acetate. The organic layer was washed with 10 % hydrochloric acid, washed with water and dried. Then, solvent was distilled off. The residue was recrystallized from benzene to obtain 0.65 g of title compound.
m.p. 215.0 - 218.0 °C

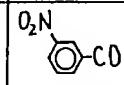
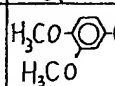
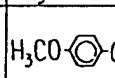
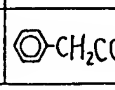
Elemental analysis (%) As $C_{16}H_{14}N_2O_4S_2$			
Calculated	C 53.02	H 3.89	N 7.73
Observed	C 53.29	H 3.86	N 7.75

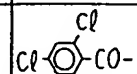
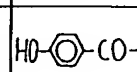
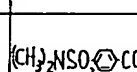
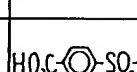
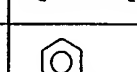
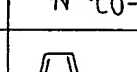
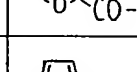
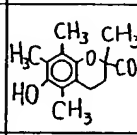
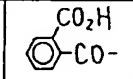
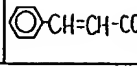
Example 4 through 51

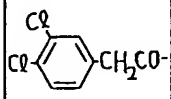
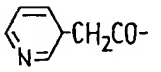
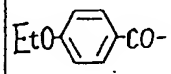
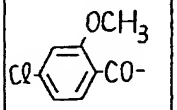
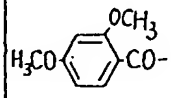
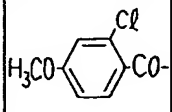
By the similar methods to Example 1 through 3, following compounds were obtained.

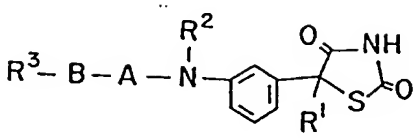


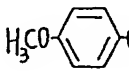
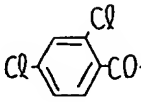
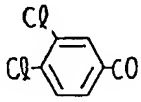
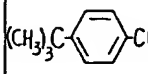
Example	R^3-B-A-	R^1	R^2	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
4		H	H	214~215	CH_3CN	$C_{16}H_{11}N_3O_5S$ C:53.78 H:3.10 N:11.76 53.74 3.05 11.78
5		H	H	266~269	Dioxane	$C_{16}H_{11}BrN_2O_3S$ C:49.12 H:2.83 N:7.16 49.20 2.92 6.88
6		H	H	245~250	$CHCl_3$	$C_{16}H_{11}ClN_2O_3S$ C:55.42 H:3.20 N:8.08 55.19 3.15 7.78
7		H	H	234~235	$CHCl_3$	$C_{17}H_{14}N_2O_4S$ C:59.64 H:4.12 N:8.18 59.30 4.07 7.98
8		H	H	239~241	$CHCl_3$	$C_{16}H_{11}FN_2O_3S$ C:58.18 H:3.36 N:8.48 58.24 3.42 8.28
9		H	H	245~250	$CHCl_3$	$C_{17}H_{14}N_2O_3S$ C:62.56 H:4.32 N:8.58 62.35 4.34 8.47
10		H	H	286~289	$CHCl_3$	$C_{22}H_{16}N_2O_3S \cdot 1/5H_2O$ C:67.40 H:4.22 N:7.16 67.49 4.22 7.08
11		H	H	275~278	Dioxane	$C_{18}H_{17}N_3O_3S$ C:60.83 H:4.82 N:11.82 60.60 4.83 11.64
12		H	H	275~276	$CHCl_3$	$C_{17}H_{11}F_3N_2O_3S$ C:53.68 H:2.92 N:7.37 53.37 2.84 7.40
13		H	H	272~275	$CHCl_3$	$C_{20}H_{20}N_2O_3S \cdot 1/6H_2O$ C:64.66 H:5.52 N:7.54 64.54 5.43 7.45
14		H	H	268~270	Dioxane	$C_{18}H_{14}N_2O_5S$ C:58.37 H:3.81 N:7.57 58.39 3.76 7.47
15		H	H	206~208	Et_2O	$C_{24}H_{28}N_2O_4S \cdot 1/5H_2O$ C:64.90 H:6.44 N:6.31 64.72 6.26 6.30
16		H	H	193~195	$CHCl_3$	$C_{17}H_{14}N_2O_4S$ C:59.64 H:4.12 N:8.18 59.58 4.08 8.16

Example	R^3-B-A-	R^1	R^2	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
17		H	H	244~246	Dioxane -n-hexane	$C_{16}H_{11}N_3O_5S$ C:53.78 H: 3.10 N:11.76 53.77 3.06 11.69
18		H	H	211~213	EtOH -n-hexane	$C_{17}H_{14}N_2O_3S$ C:62.56 H: 4.32 N: 8.58 62.94 4.24 8.24
19		H	H	229~231	EtOH -n-hexane	$C_{16}H_{11}N_3O_5S$ C:53.78 H: 3.10 N:11.76 53.94 3.03 11.42
20		H	H	228~230	CH_3CN	$C_{16}H_{11}ClN_2O_3S$ C:55.42 H: 3.20 N: 8.08 55.32 3.05 8.08
21		H	H	247~248	CH_3CN	$C_{16}H_{11}FN_2O_3S$ C:58.18 H: 3.36 N: 8.48 58.10 3.28 8.57
22		H	H	220~222	EtOH -n-hexane	$C_{18}H_{14}N_2O_5S$ C:58.37 H: 3.81 N: 7.56 58.54 3.90 7.43
23		H	H	240~242	$CHCl_3$	$C_{16}H_{10}Cl_2N_2O_3S$ C:50.41 H: 2.64 N: 7.35 50.22 2.50 7.37
24		H	H	256~258	Dioxane -n-hexane	$C_{16}H_{10}Cl_2N_2O_3S$ C:50.41 H: 2.64 N: 7.35 50.44 2.56 7.48
25		H	H	274~275	Dioxane -n-hexane	$C_{18}H_{16}N_2O_5S$ C:58.06 H: 4.33 N: 7.52 58.07 4.33 7.39
26		CH_3	H	179~180	EtOH	$C_{18}H_{16}N_2O_4S$ C:60.66 H: 4.52 N: 7.86 60.91 4.50 7.45
27		CH_3	H	209~210.5	EtOH	$C_{17}H_{12}Cl_2N_2O_3S$ C:51.66 H: 3.06 N: 7.09 51.78 3.00 7.02
28		H	H	229~231	CH_3CN	$C_{20}H_{14}N_2O_3S$ C:66.28 H: 3.89 N: 7.73 66.13 3.84 7.75
29		H	H	265~267	Dioxane	$C_{20}H_{14}N_2O_3S$ C:66.28 H: 3.89 N: 7.73 66.02 3.80 7.65
30		H	H	165~167	$CHCl_3$	$C_{17}H_{14}N_2O_3S$ C:62.56 H: 4.32 N: 8.58 62.49 4.30 8.53

Example	R^3-B-A-	R^1	R^2	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
31		H	CH_2CH_3	84~86 (Foamy crystal)	Column chromat.	Mass 408 (M^+)
32		H	H	289~290	EtOH -n-hexane	$C_{16}H_{11}N_2O_4S$ C:58.71 H: 3.39 N: 8.56 / 58.48 3.61 8.31
33		H	H	201~203	AcOEt -n-hexane	$C_{18}H_{17}N_3O_5S_2$ C:51.54 H: 4.08 N:10.02 / 51.93 4.15 9.95
34		H	H	273~274	EtOH -n-hexane	$C_{16}H_{12}N_2O_6S_2$ C:48.97 H: 3.13 N: 7.07 / 49.30 3.23 7.07
35		H	H	263~266	$CHCl_3$	$C_{15}H_{11}N_3O_3S$ C:57.50 H: 3.54 N:13.41 / 57.19 3.56 13.12
36		H	H	264~266	$CHCl_3$	$C_{14}H_{10}N_2O_4S$ C:55.62 H: 3.33 N: 9.27 / 55.37 3.31 9.09
37		H	H	253~255	Dioxane	$C_{14}H_{10}N_2O_3S_2$ C:52.84 H: 3.17 N: 8.80 / 52.69 3.08 8.71
38		H	H	222~223	CH_2Cl_2	$C_{23}H_{24}N_2O_5S$ C:62.71 H: 5.49 N: 6.36 / 62.29 5.37 6.31
39		H	H	211.5~212	EtOH	$C_{17}H_{12}N_2O_5S$ C:57.30 H: 3.39 N: 7.86 / 57.25 3.29 7.67
40		H	H	226~228	EtOH	$C_{18}H_{14}N_2O_3S$ C:63.89 H: 4.17 N: 8.28 / 64.01 4.22 8.27

Example	R^3-B-A-	R^1	R^2	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
41		H	H	226~228	EtOH	$C_{17}H_{14}Cl_2N_4O_3S$ C:51.66 H: 3.06 N:7.09 51.62 2.95 7.09
42		H	H	245~250	DMF-H_2O	$C_{16}H_{13}N_3O_3S\cdot\frac{1}{5}H_2O$ C:58.06 H: 4.01 N:12.69 58.06 3.94 12.76
43		H	H	279~282	DMF-H_2O	$C_{18}H_{16}N_2O_4S\cdot\frac{1}{5}H_2O$ C:60.05 H: 4.53 N:7.78 60.19 4.57 7.80
44		H	H	214~215	AcOEt	$C_{17}H_{13}ClN_2O_4S$ C:54.19 H: 3.48 N:7.43 54.13 3.40 7.35
45		H	H	245~249	MeOH	$C_{18}H_{16}N_2O_5S$ C:58.06 H: 4.33 N:7.52 58.05 4.38 7.50
46		H	H	215~217	AcOEt	$C_{17}H_{13}ClN_2O_4S$ C:54.19 H: 3.48 N:7.43 54.18 3.44 7.39



Example	R^3-B-A-	R^1	R^2	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
47		H	H	191~192	EtOH	$C_{17}H_{14}N_2O_4S$ C:59.64 H: 4.12 N: 8.18 59.92 4.11 8.10
48		H	H	115~120 Foamy crystal	Column chromat.	Mass 380 (M^+)
49		H	H	99~100 Foamy crystal	Column chromat.	Mass 380 (M^+)
50		H	H	85~ 86 Foamy crystal	Column chromat.	Mass 330 (M^+)
51		H	H	218~219	AcOEt -n-hexane	$C_{20}H_{20}N_2O_3S$ C:65.20 H: 5.47 N:7.60 64.97 5.53 7.55

Example 52

5-(4-(3,4-Dichlorobenzylideneamino)phenyl)thiazolidine-2,4-dione

Into 20 ml of ethanol were suspended 0.50 g of 5-(4-aminophenyl)-thiazolidine-2,4-dione, and, after added 0.42 g of 3,4-dichlorobenzaldehyde thereto, the suspension was refluxed for 3 hours. After cooling by standing, the crystals deposited were collected by filtration. The crude crystals were recrystallized from ethanol to obtain 0.79 g of title compound.

m.p. 216.5 - 218.0 °C

Elemental analysis (%) As $C_{16}H_{10}Cl_2N_2O_2S$			
Calculated	C 52.62	H 2.76	N 7.67
Observed	C 52.58	H 2.74	N 7.68

Example 53

5-(4-(3,4-Dichlorobenzylamino)phenyl)thiazolidine-2,4-dione

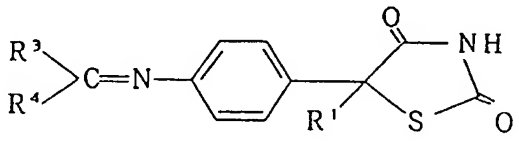
Into 40 ml of ethanol were suspended 0.40 g of 5-(4-(3,4-dichlorobenzylideneamino)phenyl)thiazolidine-2,4-dione, and, after added 0.24 g of sodium borohydride, the suspension was stirred for 2 hours at 50 °C. The reaction mixture was poured into 200 ml of water, which was extracted with ethyl acetate. The organic layer was washed with water and dried. Then, solvent was distilled off. The residue was recrystallized from iso-propanol to obtain 0.20 g of title compound.

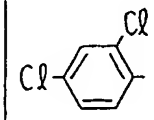
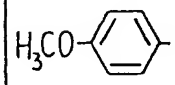
m.p. 132.0 - 133.0 °C

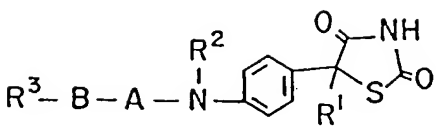
Elemental analysis (%) As $C_{16}H_{12}Cl_2N_2O_2S$			
Calculated	C 52.32	H 3.29	N 7.63
Observed	C 52.26	H 3.28	N 7.64

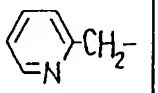
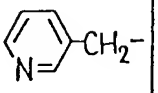
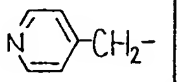
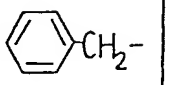
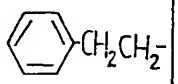
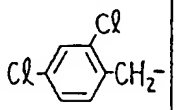
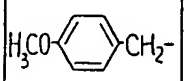
Example 54 through 62

By the similar methods to Example 52 and 53, following compounds were obtained.



Example	R^3	R^4	R^1	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
54		H	H	150~151	CH_2Cl_2 -n-hexane	$C_{16}H_{10}Cl_2N_2O_2S$ C:52.62 H: 2.76 N: 7.67 52.33 2.64 7.56
55		H	H	200~202	EtOH	$C_{17}H_{14}N_2O_3S$ C:62.56 H: 4.32 N: 8.58 62.47 4.30 8.49



Example	R^3-B-A-	R^1	R^2	Melting point (°C)	Solvent for re-crystal-lization	Elemental analysis(%) Calculated / observed
56		H	H	222~223	AcOEt	$C_{15}H_{13}N_3O_2S\cdot\frac{1}{4}H_2O$ C:59.29 H: 4.40 N:13.82 59.31 4.40 13.74
57		H	H	178~180	EtOH	$C_{15}H_{13}N_3O_2S$ C:60.18 H: 4.38 N:14.04 59.92 4.37 13.96
58		H	H	239~240	MeOH	$C_{15}H_{13}N_3O_2S\cdot\frac{1}{5}H_2O$ C:59.47 H: 4.39 N:13.87 59.29 4.23 13.90
59		H	H	181	MeOH	$C_{16}H_{14}N_2O_2S$ C:64.41 H: 4.73 N: 9.39 64.34 4.64 9.39
60		H	H	160~161	MeOH	$C_{17}H_{16}N_2O_2S$ C:65.36 H: 5.16 N:8.97 65.33 5.14 8.96
61		H	H	182~183	AcOEt	$C_{16}H_{12}Cl_2N_2O_2S$ C:52.33 H: 3.29 N: 7.63 52.48 3.22 7.61
62		H	H	150~152	CH_2Cl_2 -n-hexane	$C_{17}H_{16}N_2O_3S\cdot\frac{1}{10}H_2O$ C:61.84 H: 4.94 N:8.48 61.72 4.86 8.44

Experiment 1 Enhancement of insulin sensitivity in rats

After rats were orally administered with the compound of Example 23 once daily for 5 days at 10 mg/kg/day, they were fasted for 18 hours and then insulin was intraperitoneally injected at 0.1 unit/kg. Blood samples were collected from the tail vein 0 and 1 hour after the injection of insulin for the determination of blood glucose (Table 1).

Experiment 2 Improvement of glucose tolerance in genetically obese mice

Genetically obese mice (CS57BL ob/ob mice) were orally administered with the compound of Example 23 once daily for 5 days at 10, 30 or 100 mg/kg/day, respectively. They were fasted for 18 hours and then 2 g/kg of glucose was orally administered. Blood samples were collected from the tail vein 0, 30, 60 and 120 minutes after the administration of glucose for the determination of blood glucose (Table 2).

From these results in Tables 1 and 2, it was shown that the compound of the present invention possessed potent blood glucose lowering action.

Experiment 3 Inhibition of aldose reductase in vitro

According to the method of Hyman and Kinoshita (J. Biol. Chem., 240, 877, 1965), inhibitory activity of the compound of Example 23 on aldose reductase extracted from rat lens was investigated. As a result, the following IC_{50} value was obtained (Table 3).

Experiment 4 Inhibition on sorbitol accumulation in tissues of diabetic rats

After diabetic rats were prepared by injecting streptozotocin, they were orally administered with the compound of Example 23 once daily 2 weeks at 4, 16 or 64 mg/kg/day, respectively. The sorbitol content in nerve and retina was determined to calculate ED_{50} value (Table 4).

From these results in Table 3 and 4, it was suggested that the compound of the present invention possessed potent inhibitory activity on aldose reductase.

Table 1

Group	n	0 hour value - 1 hour value (mg %)
Reference (insulin only)	5	11. 0± 0. 8
Example 23 10mg/kg	5	19. 4 ± 1. 5 *

*: P <0. 01

Table 2

Compound	OGTT (% of control)		
	10mg/kg	30mg/kg	100mg/kg
Example 23	93. 5	89. 2	74. 1

Table 3

Compound	IC_{50} value
Example 23	9×10^{-8} M

Table 4

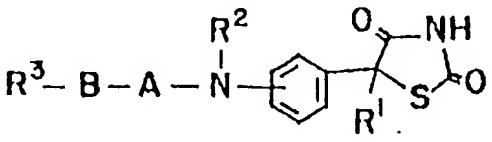
Compound	ED_{50} value (mg/kg/day)	
	Nerve	Retina
Example 23	14. 5	26. 5

Utilizability in the industry

The novel thiazolidine-2,4-dione derivatives and their salts in accordance with the invention possess superior blood sugar-lowering action together with remarkable aldose reductase-inhibitory action, thus they are useful as the drugs for the therapy and prevention of diabetes and the complication thereof.

Claims

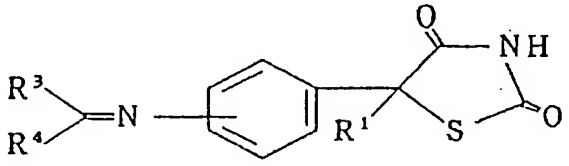
1. Thiazolidine-2,4-dione derivatives represented by a general frmula (1)



(I)

[wherein R^1 and R^2 each independently represent hydrogen atoms or lower alkyl groups, R^3 denotes a phenyl group, naphthyl group, benzoyl group or 5-membered or 6-membered heteroring and its benzene-condensed ring, which may have one or more substituents, A denotes a carbonyl group, sulfonyl group or bonding hand, and B denotes a lower alkylene, lower alkenylene or bonding hand], or their salts.

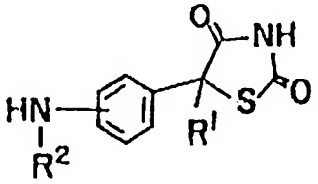
2. Thiazolidine-2,4-dione derivatives represented by a general formula (2)



(2)

[wherein R^4 denotes a hydrogen atom or lower alkyl group, and R^1 and R^3 are same as above],

3. A preparation process of thiazolidine-2,4-dione derivatives or their salts of Claim 1, characterized by reacting compounds represented by a general formula (3)



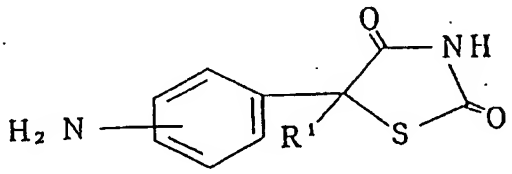
(3)

[wherein R^1 and R^2 are same as above],
or their salts with compounds represented by a general formula (4)

R^3 - B - A - Z (4)

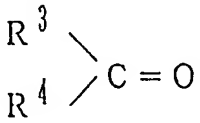
[wherein Z is an eliminating group, and R^3, A and B are same as above].

4. A preparation process of thiazolidine-2,4-dione derivatives or their salts of Claim 2, characterized by reacting compounds represented by a general formula (3a)



(3a)

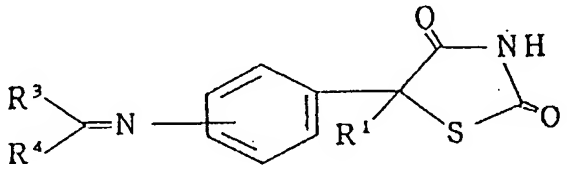
[wherein R^1 is same as above],
or their salts with compounds represented by a general formula (5)



(5)

[wherein R^3 and R^4 are same as above].

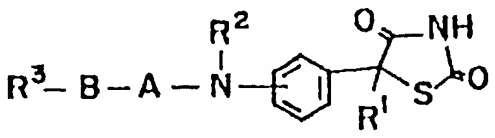
5. A preparation process of thiazolidine-2,4-dione derivatives or their salts of Claim 1, R^2 being hydrogen atom, A being bonding hand and B being lower alkylene, characterized by reducing compounds represented by the general formula (2)



(2)

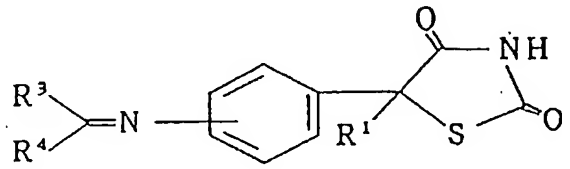
[wherein R^1, R^3 and R^4 are same as above].

6. A blood sugar-lowering agent having at least one kind of thiazolidine-2,4-dione derivatives represented by the general formula (1)



(1)

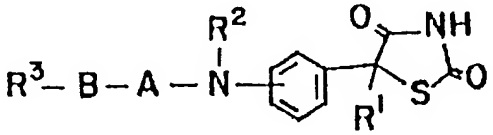
[wherein R^1, R^2, R^3, A and B are same as above],
or their salts, or thiazolidine-2,4-dione derivatives represented by the general formula (2)



(2)

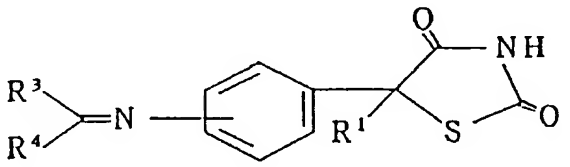
[wherein R^1, R^3 and R^4 are same as above],
or their salts are effective ingredient(s).

7. An aldose reductase-inhibitary agent having at least one kind of thiazolidine-2,4-dione derivatives represented by the general formula (1)



(1)

[wherein R^1, R^2, R^3, A and B are same as above],
or their salts, or thiazolidine-2,4-dione derivatives represented by the general formula (2)



(2)

[wherein R^1, R^3 and R^4 are same as above],
or their salts as effective ingredient(s).

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP92/00189

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl[5] C07D277/34, C07D417/12, A61K31/425, A61K31/44

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07D277/34, C07D417/12, A61K31/425, A61K31/44

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	JP, A, 57-28073 (Takeda Chemical Industries, Ltd.), February 15, 1982 (15. 02. 82), (Family: none)	1-7
Y	JP, A, 59-137474 (Pfizer Inc.), August 7, 1984 (07. 08. 84), (Family: none)	1-7
A	JP, A, 55-22636 (Takeda Chemical Industries, Ltd.), February 18, 1980 (18. 02. 80), & EP, A, 8203 & US, A, 4340605	1-7

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
April 22, 1992 (22. 04. 92)	May 12, 1992 (12. 05. 92)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	